Biomarkers of Cognitive Impairment in Children with HIV: Update on IMPAACT NWCS 604

David Bearden MD
Assistant Professor, University of Rochester School of Medicine, Division of Child Neurology

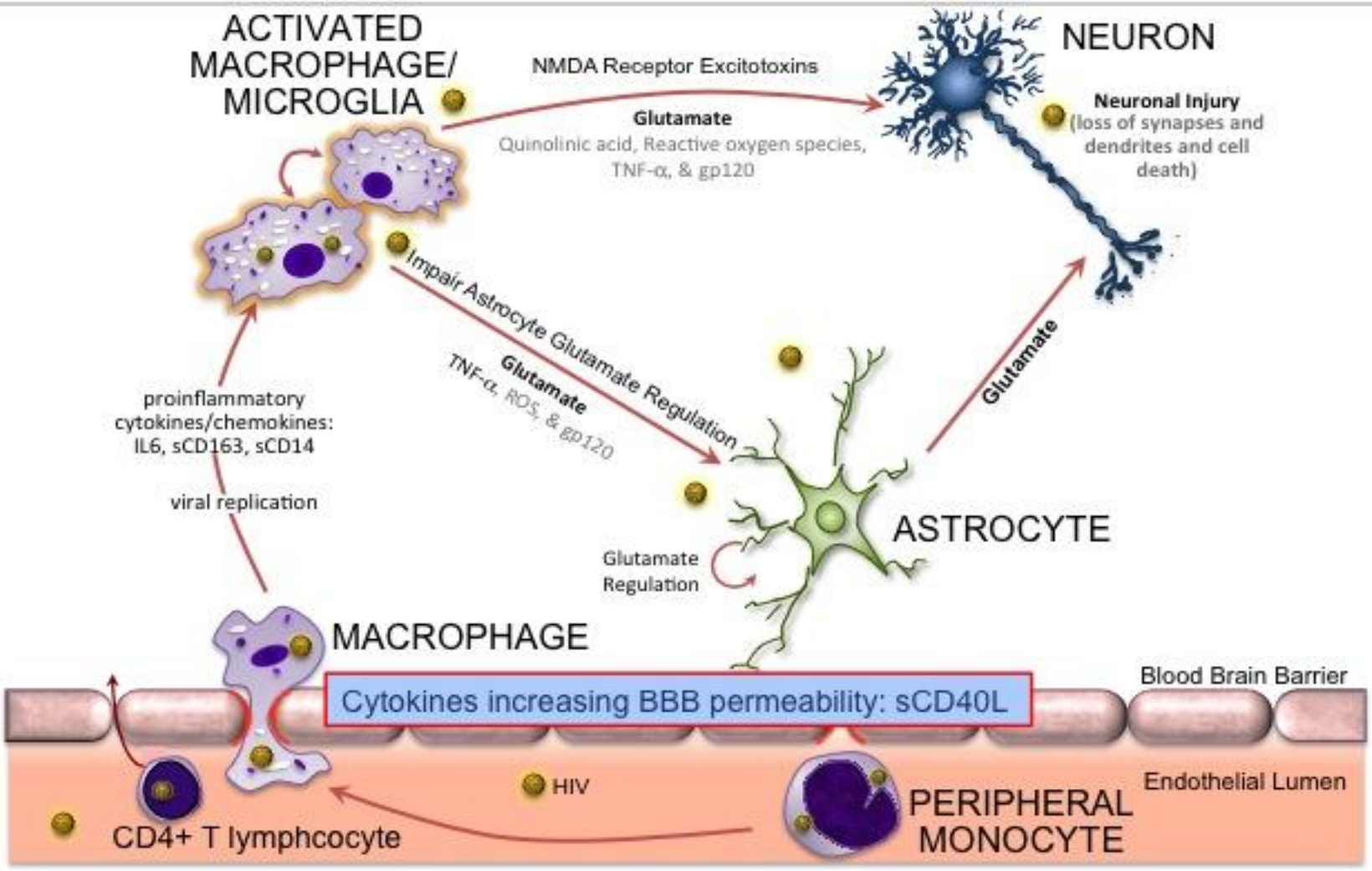
Acknowledgements and Disclosures

- This research is supported by the IMPAACT Early Career Investigator Mentored Research Award.
- Dr. Bearden has served as a consultant for Q-state Biosciences and Abbvie
- Dr. Steven Douglas is the research mentor for this award.

Background

- Cognitive impairment is common in children and adolescents with HIV in resource-limited settings, affecting 20-70% of children
- Incident cognitive impairment is relatively uncommon in cART treated children, affecting less than 10% of children
- Systemic inflammation and immune activation is hypothesized to play a key role in the pathogenesis of HIV-associated cognitive impairment

HIV-associated neurocognitive disorders pathogenesis: HIV entry and neurotoxicity in central nervous system



Adapted from Gill & Kolson, *Crit. Rev. Immunol.* (2013).

Can inflammatory biomarkers predict risk of cognitive impairment?

- **Questions:**

1. Do cART treated children have elevated markers of immune activation compared to HIV-exposed uninfected controls?

2. What is the temporal profile of key biomarkers?

- **Hypothesis:** Children with HIV on cART will have increased levels of Tumor Necrosis Factor-Alpha (TNF-α), Tumor Necrosis Factor-Alpha Receptor II (TNFRII), soluble CD163 (sCD163), soluble CD14 (sCD14), and soluble CD40 ligand (sCD40L) compared to exposed uninfected controls.

Methods

Parameters	HIV infected	HIV exposed uninfected controls
Samples	219C 74 pre-cART samples 75 post-cART samples	• 219 C • 24 samples age matched to post-cART group
Inclusion criteria	8-18 years Starting cART and virally suppressed during period of study	8-18 years
Exclusion criteria	Horizontal transmission Cognitive decline	None

Characteristics of cases and control subjects

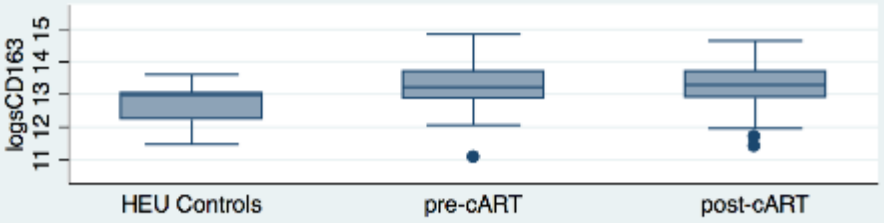
Variable	PHIV on cART (n=75)	Controls (n=24)	P-value
Male sex	11 (46%)	27 (39%)	0.53
Black Race	42 (56%)	14 (58%)	0.66
Hispanic ethnicity	26 (35%)	7 (29%)	0.66
Born in U.S.	66 (88%)	24 (100%)	**0.08**
Low maternal education	20 (32%)	10 (42%)	0.66

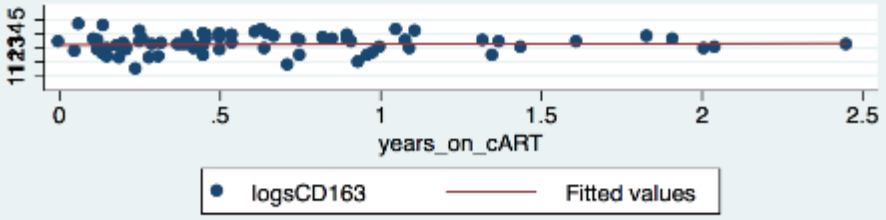
Comparison between cases and controls

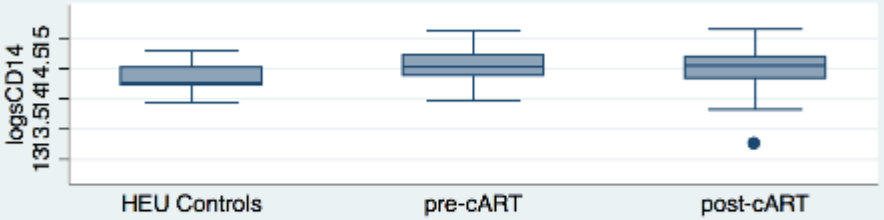
Biomarker	Cases	Controls	Comparison	Beta	P-value
sCD163	594	436	↑	0.52	**<0.001***
sCD14	2,079	1,567	↑	0.18	**0.006***
TNFR2	2447	2388	⇔	.003	0.783
TNF	21.8	27.0	↓	-0.28	0.001*
CD40 ligand	1017	1949	↓	-0.36	0.037

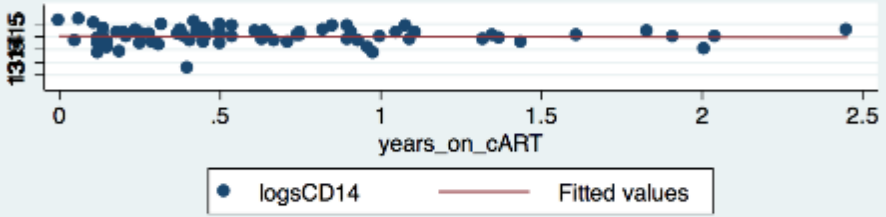
Comparison between cases and controls

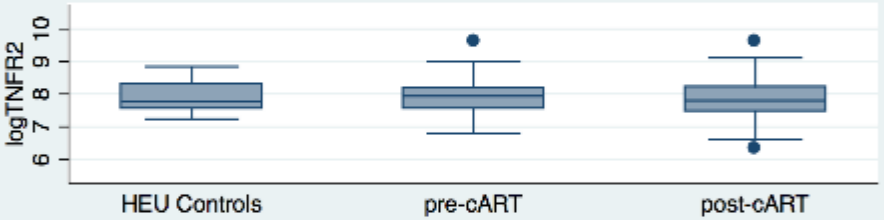
Biomarker	Cases	Controls	Comparison	Beta	P-value
sCD163	594	436	↑	0.52	**<0.001***
sCD14	2,079	1,567	↑	0.18	**0.006***
TNFR2	2447	2388	⇔	.003	0.783
TNF	21.8	27.0	↓	-0.28	0.001*
CD40 ligand	1017	1949	↓	-0.36	0.037

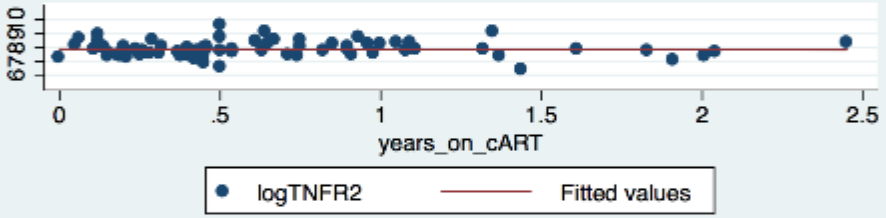

logsCD163
11 12 13 14 15
HEU Controls
pre-cART
post-cART

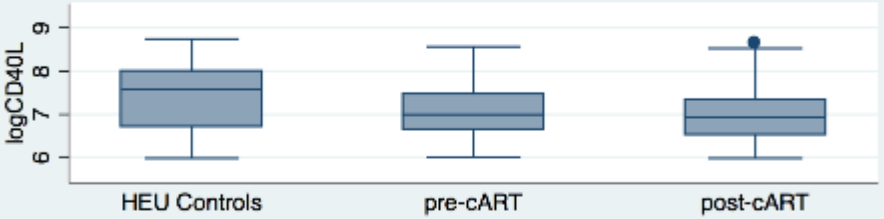

1 2 3 4 5
0
.5
1
1.5
2
2.5
years_on_cART
logsCD163
Fitted values

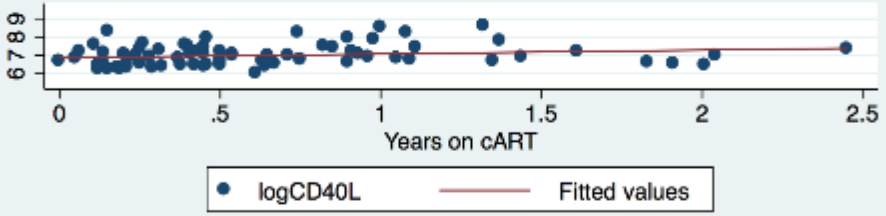

logsCD14
13 13.5 14 14.5 15
HEU Controls
pre-cART
post-cART

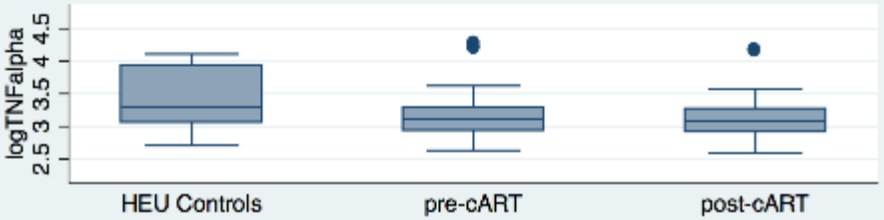

13 13.5 14 14.5 15
0
.5
1
1.5
2
2.5
years_on_cART
logsCD14
Fitted values

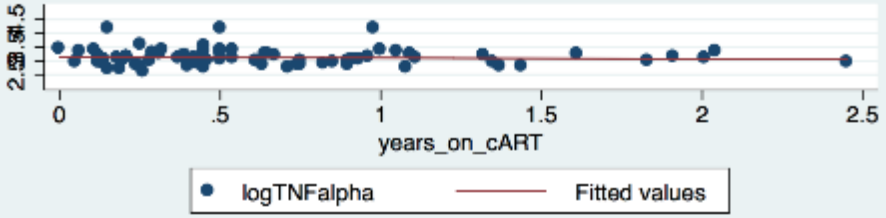

logTNFR2
6 7 8 9 10
HEU Controls
pre-cART
post-cART


6 7 8 9 10
0
.5
1
1.5
2
2.5
years_on_cART
logTNFR2
Fitted values


logCD40L
6 7 8 9
HEU Controls
pre-cART
post-cART


6 7 8 9
0
.5
1
1.5
2
2.5
Years on cART
logCD40L
Fitted values


logTNFalpha
2.5 3 3.5 4 4.5
HEU Controls
pre-cART
post-cART


2 2.5 3 3.5 4 4.5
0
.5
1
1.5
2
2.5
years_on_cART
logTNFalpha
Fitted values

Biomarkers and Cognitive Decline

- **Goal: To identify biomarkers and clinical characteristics associated with a high risk of cognitive decline in children and adolescents with HIV treated with cART**
- **Hypothesis:** Children with cognitive decline will have elevated markers of immune activation including Tumor Necrosis Factor-Alpha (TNF-α), soluble CD163 (sCD163), soluble CD14 (sCD14), and soluble CD40 ligand (sCD40L) compared to controls without decline.
- .

Methods

	Cases (n=65)	Controls (n=65)
Parameters	HIV infected with IQ drop >15 points	HIV infected with normal cognition
Inclusion criteria	8-18 years on cART achieving viral suppression	same
Exclusion criteria	History of CNS infection Diabetes Chronic kidney disease Pregnancy	Same

Characteristics of cases and controls

Variable	Controls (n=65)	Cases (n=65)	P-Value
Age at Baseline	9.7 (7-12)	9.2 (8-11)	0.9
Age at time of decline	12.2 (10.9-13.5)	12.2 (11-13.4)	1
Hispanic ethnicity	**12 (18%)**	**28 (43%)**	**0.02**
Born in U.S.	**93%**	**80%**	**0.03**
Viral load timepoint 2	**<400 (<50-1757)**	**1027 (400-10,033)**	**0.006**
CD4 timepoint 1	950 (572-1180)	737 (496-1052)	0.86
CD4 timepoint 2	**726 (515-1022)**	**655 (439-757)**	**0.03**
Mean reported adherence	**100**	**88%**	**0.002**

Clinical risk factor for cognitive decline

Risk Factor	Odds ratio	P-Value
CD4 count <200	4 (0.9- 18.9)	0.08
History of CDC class C diagnosis	1.7 (0.67-4.4)	0.26
Detectable viral load	2.6 (1.1-5.5)	**0.02***
Hispanic ethnicity	3 (1.3-6.7)	**0.007***
Born outside U.S.	3.3 (1.1-10.0)	**0.04***
Caregiver education < 12 years	3 (1.2-7.6)	**0.02***
Clinical Risk Score	1.9 (1.3-2.6)	**0.001***

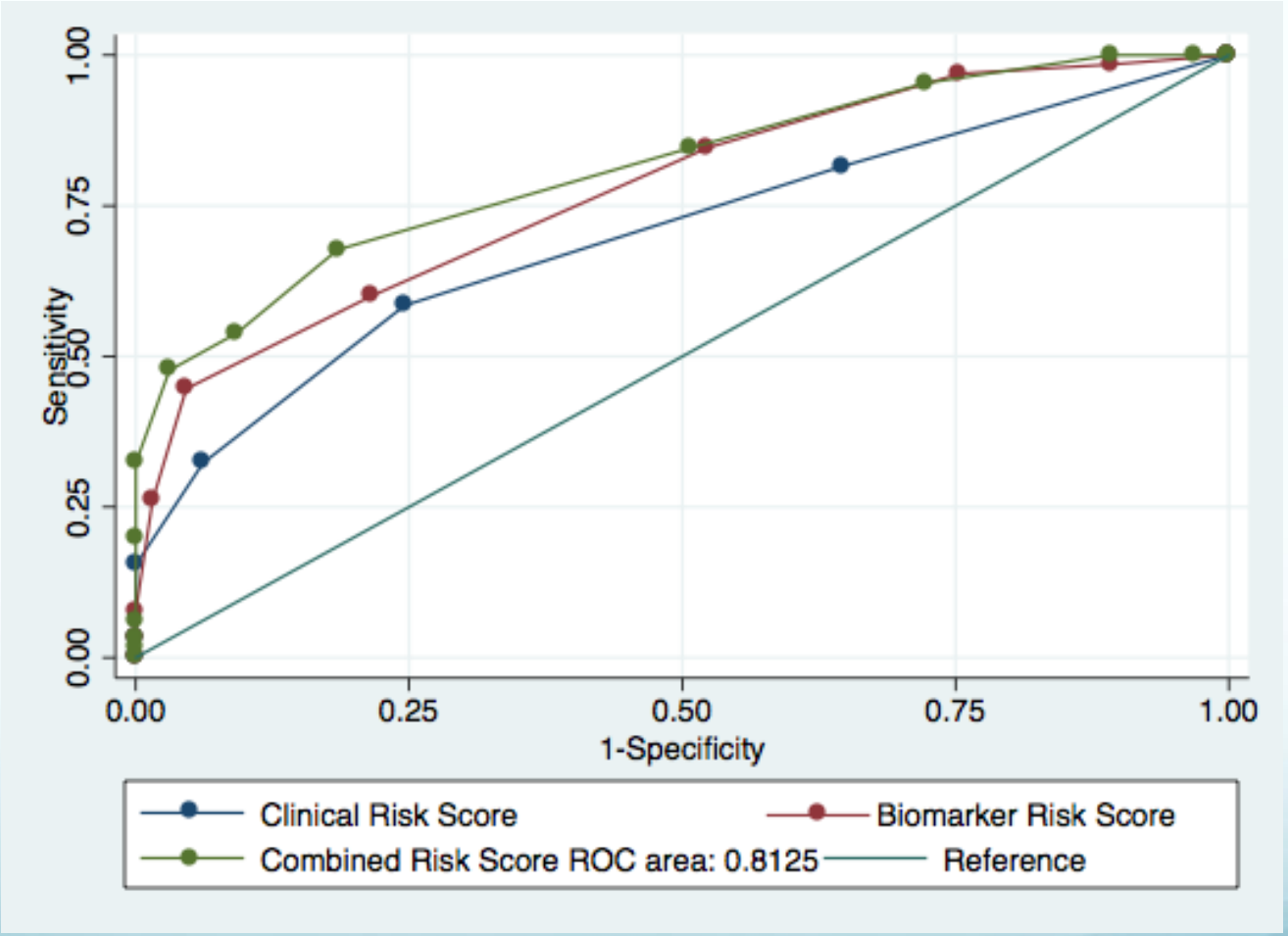
Mean biomarker levels in cases compared to controls

Primary Biomarkers	Timepoint 1		Timepoint 2		Change over time	
	Beta	**P-value**	**Beta**	**P-value**	**Beta**	**P value**
sCD163	0.13	0.59	↑0.17	**0.02***	-33446	0.82
sCD14	-0.22	0.06	0.07	0.36	↑**44492 0**	0.05*
TNFR2	0.13	0.39	0.15	0.09	60	0.89
sCD40L	-0.15	0.43	.22	0.07	↑**546**	0.04*
TNF-alpha	↑**0.12**	**0.04***	.04	0.36	-1.03	0.19

Biomarkers and cognitive decline

Variable	Odds Ratio	P-value	R^2
CRP	2.5 (1.2-5.2)	**0.01***	0.07
TNFR1	4 (1.3-12.0)	**0.01***	0.08
TNFR2	1.8 (0.9-3.7)	0.09	0.03
sCD163	2.3 (1.1-4.6)	**0.02***	0.06
sCD14	1.6 (0.73-3.8)	0.23	0.02
sCD40L	2.3 (1.1-4.6)	**0.02***	0.06
Biomarker Risk Score	2 (1.4-2.8)	**<0.001***	0.34

Comparison of predictive models



Future Directions

- In the upcoming HIV-associated Neurocognitive Disorders in Zambia (HANDZ) study we will prospectively test our predictive model
- Goal is early detection of patients at risk for neurocognitive decline
- Eventual trials of neuroprotective agents

Questions?

- Thanks to:
- Steve Douglas
- Paige Williams, Allison Agwu, Russ Van Dyke, Sharon Nichols, Laura Schankel, Dennis Kolson, Alex Gill
- IMPAACT Complications Committee
- PHACS and the 219C team